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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/996,738 | 11/30/2001 | Philip Gotwals | A076 US | 4464 |

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| EXAMINER |
|---|
| HADDAD, MAHER M |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | |

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DATE MAILED: 03/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/996,738 | GOTWALS ET AL. | |
| | Examiner | Art Unit | |
| | Maher M. Haddad | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 01/05/04, is acknowledged.

2. Claims 1-7 are pending and under consideration in the instant applicantion.

3. In view of the amendment filed on 01/05/04, only the following rejections are remained.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

5. Claims 1-7 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrases "equivalent thereof" and "a dosage of between about 10mg to about 250 mg administered over a dosing period of between about one to about seven days" claimed in claim 1, lines 5-9 represent a departure from the specification and the claims as originally filed for the same reasons set forth in the previous Office Action mailed 10/21/03.

Applicant's arguments, filed 1/5/04, have been fully considered, but have not been found convincing.

Applicant points to page 9, lines 2-9 for support for "equivalent thereof" and asserts that the application as originally filed disclosed methods that enabled those of ordinary skill to determine sequences equivalent to SEQ ID NO: 8. Further Applicant points to page 19, lines 3-8 for support for "a dosage of between about 10mg to about 250 mg administered over a dosing period of between about one to about seven days. Applicant argues that the recited dosage ranges fall within the ranges specified in the application as originally filed.

Since specification does not *Ipsis verbis* describe the phrases "equivalent thereof" and "a dosage of between about 10mg to about 250 mg administered over a dosing period of between about one to about seven days" and the specification on page 9, lines 2-9, discloses antibodies to the I domain of the $\alpha$ chain ($\alpha 1\beta 1$, $\alpha 2\beta 2$, $\alpha L\beta 2$, $\alpha M\beta 2$, $\alpha X\beta 2$) but does not provide an antibodies to the epitope of the 8 amino acids of Val-Gln-Arg-Gly-Gly-Arg (SEQ ID NO:8). Similarly, the specification on page 19, lines 38, discloses dosage ranges of 0.001 and about 100 mg/kg, 0.1-50 mg/kg and 0.1-20mg/kg of body weight at intervals of every 1-14 days, but no specific ranges of a dosage of between about 10mg to about 250 mg administered over a dosing period of between about one to about seven days is disclosed.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

*(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

7. Claims 1-7 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,788,966 (IDS Ref. No. AA) as is evidenced by the specification disclosed on page 36, lines 7-8 for the same reasons set forth in the previous Office Action mailed 10/21/03.

Applicant's arguments, filed 1/5/04, have been fully considered, but have not been found convincing.

Applicant contends that despite all of the differences between Chess and the claimed invention, the Examiner finds the claims obvious because he believes that they merely reflect optimization of dosages and durations of known treatments. Applicant contends that such position misconstrues the claims and ignores the differences between Chess and the claimed invention.

However, it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal concentrations of components because concentration is an art-recognized result-effective variable which would have been routinely determined and optimized in the pharmaceutical art. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP §§ 2144.05 part II A.

Applicant argues that (the `966 patent) Chess 's disclosure that (1) the synovial fluid of arthritis patients expresses enhanced levels of VLA-1[1] (2) mAb 1B3.1 affects the interaction of VLA-1 and T cells in conditions where enhanced levels of VLA-1 are noted, and (3) that the synovial fluid of arthritis patients expresses enhanced levels of VLA-1, do not equate to the treatment regimen of the claims, in which a defined epitope is targeted, defined dosages are administered, and defined clinical endpoints are achieved. Applicant contends that the key limitations of the pending claims are not minor variations of a specific treatment method disclosed in Chess. Cf Haynes International, Inc. v. Jessop Steel Co., 28 U.S.P.Q.2d 1652 (Fed. Cir. 1993), on reh'g, 29 U.S.P.Q.2d 1958 (Fed. Cir. 1994).

However, the `966 patent teaches the same method for the treatment of arthritis comprising administering to a human a MAb IB3.1. The target antigen of MoAb 1B3.1 consists of proteins of 200 and 110 kDa that are identical to VLA-1 proteins (see col. 8, lines 38-45 in particular), which is the same as the claimed product (functional antibody). As is evidenced by the specification on page 36, lines 7-8, that all the function-blocking mAbs recognizes the chimeric I domain.

Applicant contends that the manipulative differences between the steps of each of the pending claims and the disclosure of Chess constitute a detailed improvement over Chess. These differences establish that a significant aspect of the claimed invention is unexpected in light of Chess and refute the notion that the claims are unpatentable as obvious. See Bristol Myers Squibb Co. v. Ben Venue L laboratories, Inc., 58 U.S.P.Q. 2d 1508 (Fed. Cir. 2001),. In re Eli Lilly & Co., 14 U.S.P.Q. 2d 1741 (Fed. Cir. 1990) "*prima facie* obviousness where claim not limited to details or improvements not shown in the art).

However, a person having ordinary skill in the art would have found it obvious to determine the optimum values of result-effective variables known in the art. Therefore, applicant failed to rebut *prima facie* showing obviousness absent objective evidence such as side-by-side testing that would address the thrust of the examiner's rejection and establish unexpected results. Ex parte Raske, 28 USPQ2d 1304 (BPAI 1993).

In response to applicant's argument that there is no motivation in the art to modify Chess to result in the administration of an antibody or antibody fragment in a dosage of between about 10 mg to about 250 mg administered over a dosing period of between about one to about seven days to provide a decrease in arthritic score of about 65% or greater when compared to a control antibody treated subject, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art . In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In this case, the '966 patent teachings provide clear direction, motivation and expectation of success in treating arthritis with VAL-1 I domain-specific antibodies. The '966 patent teaches a method for treating arthritis that is associated with elevated levels of VLA-1 with antibody 1B3.1 that inhibits collagen binding to VLA-1.

8. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,788,966 (IDS Ref. No. AA) in view of Riikonen et al (Biochemical and Biophysical Research Communication 209:205-212, 1995) and Fabbri et al (IDS Ref. No. CB) for the same reasons set forth in the previous Office Action mailed 10/21/03.

Applicant's arguments, filed 1/5/04, have been fully considered, but have not been found convincing.

Applicant contends that the premise of this rejection is flawed because it assumes, without any support, that key claim limitations relating to epitope, dosage, and therapeutic endpoint were

somehow known as the result of Chess, Riikonen, and Fabri. Chess 's disclosure that monoclonal antibody 1B3.1 binds to a distinct VLA-1 epitope; Riikonen 's disclosure that the mAb SR-84 blocks the function of $\alpha 1\beta 1$ integrin and that in HeLa cells $\alpha 1\beta 1$ integrin acts as a receptor for certain types of collagen', and Fabbri 's disclosure that the FB12 mAb is functional in that it blocks the adhesion of activated T lymphocytes to fibronectin, collagen type IV and laminin do not disclose the specific epitope target, dosages, and therapeutic endpoints recited in the pending claims. Further, Applicant argues that the epitope target, dosage, and duration of treatment claim limitations are not "prior art elements (that) will perform their expected functions to achieve their expected results when combine[d] for their common known purpose." Office Action, page 6. Applicant agrues that Fabbri stated that FB12 mAb "may represent a useful reagent for the study of the biological function of $\alpha 1$-1 integrin 1 domain"; the reference did not specify that the FB12 mAb was a therapeutic agent that could target a specific epitope of VLA-I to achieve a defined clinical result. Fabbri recognized that FB12 mAb might bind to ECM. However, by the time Fabbri reached this conclusion, Rilkonen had published that ECM is found in the synovial lymphocytes of patients with rheumatoid arthritis. Riikonen did not lead Fabbri to conclude that FB12 mAb could be used to treat rheumatoid arthritis. Nor did Chess cite Fabbri or Rilkonen in support of Chess 's disclosure of therapeutic methods and compositions.

However, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and not is it that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). See MPEP 2145.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin , 170 USPQ 209 (CCPA 1971).

9. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,788,966 (IDS Ref. No. AA) in view of Riikonen et al (Biochemical and Biophysical Research Communication 209:205-212, 1995) for the same reasons set forth in the previous Office Action mailed 10/21/03.

Applicant's arguments, filed 1/5/04, have been fully considered, but have not been found convincing.

Applicant contends that in making this rejection, the Examiner ignores the key epitope, dosage, and clinical endpoint limitations of the claims, and asserts that "he is free to do" because those limitations are mere optimizations of known parameters. Neither Chess nor Riikonen disclose any of the key claim limitations. Even if Chess and Rilkonen could be combined as suggested, they still would not yield those limitations and would not lead to the claimed methods of

treatment. It is therefore incorrect to characterize Applicants' claimed invention as an optimization and combination of parameters found in one or more prior art references.

In contrast to applicant's assertions that the examiner is free to ignore the key epitope, dosage and clinical endpoint limitations of the claim; the examiner has relied upon adequate explanations with supporting evidence to maintain the rejection of record under U.S.C 103(a). After evidence or arguments are submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument.

10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
March 11, 2004

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